THE EFFECT OF MYOGLOBIN-FACILITATED OXYGEN TRANSPORT ON THE BASAL METABOLISM OF PAPILLARY MUSCLE

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ABSTRACT A mathematical model of oxygen diffusion into cylindrical papillary muscles is presented. The model partitions total oxygen flux into its simple and myoglobin-facilitated components. The model includes variable sigmoidal, exponential, or hyperbolic functions relating oxygen partial pressure to both fractional myoglobin saturation and rate of oxygen consumption. The behavior of the model was explored for a variety of saturation- and consumption-concentration relations. Facilitation of oxygen transport by myoglobin was considerable as indexed both by the elevation of oxygen partial pressure on the longitudinal axis of the muscle and by the fraction of total oxygen flux at the muscle center contributed by oxymyoglobin. Despite its facilitation of oxygen flux at the muscle center, myoglobin made only a negligible contribution to the total oxygen consumption averaged over the muscle cross-section. Hence the presence of myoglobin fails to explain either the experimentally determined basal metabolism–muscle radius relation or the stretch effect observed in isolated papillary muscle.

INTRODUCTION

Myoglobin enhances intracellular oxygen flux at low partial pressures of oxygen (for reviews see Kreuzer, 1970; Wittenberg, 1970). It is unknown whether it contributes appreciably in supplying oxygen to the central core of a papillary muscle that is isolated from its blood supply and bathed in saline. An assessment of its contribution is sought by mathematical simulation of myoglobin-facilitated oxygen diffusion into a cylindrical muscle. The purpose of the simulation is twofold: to quantify the contribution made by myoglobin in supplying oxygen to papillary muscles in vitro, and to see if this contribution can explain the observed basal metabolism–muscle radius relation (Loiselle and Gibbs, 1983). The mathematical model differs from most previous formulations in assuming a nonlinear dependence of oxygen consumption upon oxygen concentration.

GLOSSARY OF TERMS AND TYPICAL VALUES

r_o	muscle radius (mm)
r	radial location (variable)
p_o	partial pressure of oxygen at surface of muscle (torr)
p	local partial pressure of oxygen (variable)
p_a	partial pressure of oxygen on central longitudinal axis
PO_2	partial pressure of oxygen
m	metabolic rate (expressed in mW/g assuming an energetic equivalent of oxygen of 20 kJ/liter)
m_o	metabolic rate that would prevail at the periphery of the muscle given a sufficiently high p_o
$\overline{m}$	mean metabolic rate averaged over the muscle cross-sectional area
S	fraction of total myoglobin that is saturated with O_2
$p_{50,m}$	partial pressure of oxygen yielding half-maximal (50%) metabolism
$p_{50,S}$	partial pressure of oxygen yeilding half-maximal (50%) saturation of myoglobin
Mb; MbO_2	myoglobin; oxymyoglobin
m_2; S_2	parameters defining the sigmoidal and exponential relations between oxygen partial pressure and metabolism; myoglobin saturation
n_m; n_S	parameters defining the sigmoidal (Hill equation) and hyperbolic relations between oxygen partial pressure and metabolism; myoglobin saturation
σ_{O_2}	solubility of oxygen in muscle tissue (1.323×10^{-9} mol $O_2 \cdot cm^{-3} \cdot torr^{-1}$ at 30°C)
c_{Mb}	concentration of myoglobin in cardiac muscle (either 0 or 2.8×10^{-7} mol $\cdot cm^{-3}$ for absence and presence of facilitated diffusion, respectively)
D_{O_2}; D_{Mb}	diffusion constants for O_2; and both Mb and MbO_2 in muscle tissue (1.5×10^{-5} and 0.7×10^{-6} $cm^2 \cdot s^{-1}$, respectively)
J_{O_2}; J_{MbO_2}; J	flux of oxygen by simple; myoglobin-facilitated; or combined ($J = J_{O_2} + J_{MbO_2}$) diffusion ($W \cdot cm^{-2}$)

METHODS

The papillary muscle is modelled as a homogeneous solid cylinder into which O_2 diffuses, from a source of constant PO_2, by both simple and facilitated means (i.e., as molecular oxygen and oxymyoglobin, respectively). The length of the cylinder is great with respect to its radius so that only radial diffusion need be considered. The tissue within the cylinder respires (i.e., consumes oxygen) at a rate that depends on the local partial pressure of oxygen. Two distinct analytical forms of this dependence are examined. The limiting case of one is exponential and of the other is

hyperbolic. Only steady-state (i.e., non-time-dependent) solutions are of interest.

The formal development of the mathematical model closely follows that of Murray (1974). The reaction between oxygen and myoglobin, Mb, is given by:

$$n\mathrm{O_2} + \mathrm{Mb} \underset{k_b}{\overset{k_f}{\rightleftharpoons}} \mathrm{MbO_2}, \tag{1}$$

where k_f and k_b are the forward and backward reaction rate constants, respectively, and the stoichiometry of the reaction is such that $n = 1$ (Wittenberg, 1970). If S is the proportion of Mb molecules saturated with oxygen, that is

$$S = \frac{[\mathrm{MbO_2}]}{[\mathrm{Mb}] + [\mathrm{MbO_2}]}, \tag{2}$$

then the steady-state rate of reaction 1, ρ, is given by:

$$\rho = k_f (1 - S)\,[\mathrm{Mb}]\,[\mathrm{O_2}] - k_b S\,[\mathrm{MbO_2}]. \tag{3}$$

In the "one-dimensional" cylinder of interest, the steady-state diffusion of free oxygen is given by

$$D_{\mathrm{O_2}} \frac{1}{r}\frac{\mathrm{d}}{\mathrm{d}r}\left(r\frac{\mathrm{d}[\mathrm{O_2}]}{\mathrm{d}r}\right) - \rho = m(p), \tag{4}$$

where $D_{\mathrm{O_2}}$ is the diffusivity of oxygen, r is the radial location, and m is the metabolic rate of oxygen consumption, a function of local tissue partial pressure of oxygen, p. The steady-state diffusion of bound oxygen is given by

$$[\mathrm{Mb}]\, D_{\mathrm{Mb}} \frac{1}{r}\frac{\mathrm{d}}{\mathrm{d}r}\left(r\frac{\mathrm{d}S}{\mathrm{d}r}\right) + \rho = 0. \tag{5}$$

Redefine $c_{\mathrm{Mb}} = [\mathrm{Mb}] + [\mathrm{MbO_2}]$ as the total concentration of myoglobin (free and bound, respectively) within the muscle. Note that

$$[\mathrm{O_2}] = \sigma_{\mathrm{O_2}} \cdot p, \tag{6}$$

where $\sigma_{\mathrm{O_2}}$ is the solubility of oxygen in saline. Then addition of Eqs. 4 and 5 and substitution of Eq. 6 yields

$$\sigma_{\mathrm{O_2}} D_{\mathrm{O_2}}\left(\frac{\mathrm{d}^2p}{\mathrm{d}r^2} + \frac{1}{r}\frac{\mathrm{d}p}{\mathrm{d}r}\right) + c_{\mathrm{Mb}} D_{\mathrm{Mb}}\left(\frac{\mathrm{d}^2S}{\mathrm{d}r^2} + \frac{1}{r}\frac{\mathrm{d}S}{\mathrm{d}r}\right) = m(p). \tag{7}$$

Eq. 7 defines the mathematical model of oxygen diffusion into a cylindrical papillary muscle. It consists of two non-interactive, additive terms, the first governing simple diffusion and the second governing myoglobin-facilitated diffusion. It implicitly assumes that oxygen solubility, total myoglobin concentration, and the diffusivity of both oxygen and myoglobin are independent of radial location, i.e., that the muscle is homogeneous. It further assumes that the diffusivities of bound and free myoglobin are identical (see Wittenberg, 1970) and that the kinetics of Eq. 1 are sufficiently rapid to permit equilibrium to be achieved between free and bound oxygen (Murray, 1974). The latter assumption is likely met when the rate of oxygen consumption is low as in the basal state of interest to this investigation.

The uniqueness of the model lies in the term $m(p)$, which governs oxygen consumption. Oxygen consumption is not independent of oxygen concentration as in many formulations (Murray, 1974; Rubinow and Dembo, 1977; Van Ouwerkerk, 1977; Fletcher, 1980; Gonzalez-Fernandez and Atta, 1982; Stroeve, 1982; but see Taylor and Murray, 1977, and de Koning et al., 1981) but is assumed to depend in some way upon local tissue oxygen partial pressure. The general form of this dependence in vivo is unknown. For the purpose of this study it will be assumed to be sigmoidal and to be described by either

$$m(p) = m_o\,(1 - e^{-m_1 p})^{m_2} \tag{8a}$$

or by the Hill equation

$$m(p) = m_0 \frac{(p/p_{50,\mathrm{m}})^{n_\mathrm{m}}}{1 + (p/p_{50,\mathrm{m}})^{n_\mathrm{m}}}. \tag{8b}$$

Note that if m_2 (Eq. 8a) or n_m (Eq. 8b) is set to unity, then the dependence reduces to simple exponential and hyperbolic, respectively.

The precise form of the dependence in vivo of myoglobin saturation upon oxygen partial pressure is also unknown (Wittenberg, 1970; Wittenberg et al., 1975; Cole et al., 1978). But it may again be approximated by a sigmoidal relation described by either

$$S(p) = (1 - e^{-S_1 p})^{S_2} \tag{9a}$$

or by the Hill equation

$$S(p) = \frac{(p/p_{50,\mathrm{S}})^{n_\mathrm{S}}}{1 + (p/p_{50,\mathrm{S}})^{n_\mathrm{S}}}. \tag{9b}$$

Note that, in either case, as $p \to \infty$, $S(p) \to 1$ (i.e., full saturation), as required, and if $S_2 = 1$, then Eq. 9a reduces to simple exponential form. If $n_\mathrm{S} = 1$, then Eq. 9b reduces to the hyperbolic form commonly used to fit experimentally measured myoglobin saturation data. It is to be emphasized that Eqs. 8 and 9 are essentially descriptive in nature, i.e., they provide two possible analytical descriptions of the dependence of metabolism and oxymoglobin saturation, respectively, upon local PO_2. The only parameter with a rigorous definition is p_{50}. Hence it is helpful to recast parameters m_1 and S_1, in Eqs. 8a and 9a, respectively, in terms of their corresponding p_{50} values. This reformulation is achieved (in the case of metabolism) by

$$m_1 = \frac{1}{p_{50,\mathrm{m}}} \ln \frac{1}{[1 - (1/2)^{1/m_2}]}, \tag{10}$$

where $p_{50,\mathrm{m}}$ is the partial pressure of oxygen that achieves half-maximal oxygen consumption ($m_o/2$). An analogous equation yields S_1 in terms of the oxygen partial pressure that achieves half-maximal saturation ($p_{50,\mathrm{S}}$).

One example of each $m = m(p)$ and $S = S(p)$ relation is shown in Fig. 1 where the p_{50} values are made explicit. Note that the metabolism relation, $m(p)$, must lie to the left of the myoglobin relation, $S(p)$, if significant facilitation of oxygen flux is to occur. For this reason it is not sensible to mix the exponential and hyperbolic forms because, for any given value of p_{50}, the hyperbolic form lies to the left of the exponential form if $p < p_{50}$ and to the right of (and below) it when $p > p_{50}$, as comparison of a and b in Fig. 1 shows.

An existing computer program that uses a Runge–Kutta method of solving the diffusion equation in the absence of facilitation (Loiselle, 1982, 1985*a*) was modified to solve Eq. 7, where $m(p)$ is given by Eq. 8. Solution is subject to the following boundary conditions:

$$p(r_o) = p_o$$

and

$$\frac{\mathrm{d}p}{\mathrm{d}r}(0) = 0. \tag{11}$$

The result yields p and S as functions of r, i.e., the oxygen partial pressure and myoglobin saturation at various radial locations within the muscle.

Given the solution of Eq. 7, subject to the boundary conditions (Eq. 11), the net flux of oxygen at any radial location within the muscle can be partitioned into its simple and myoglobin-facilitated components, respec-

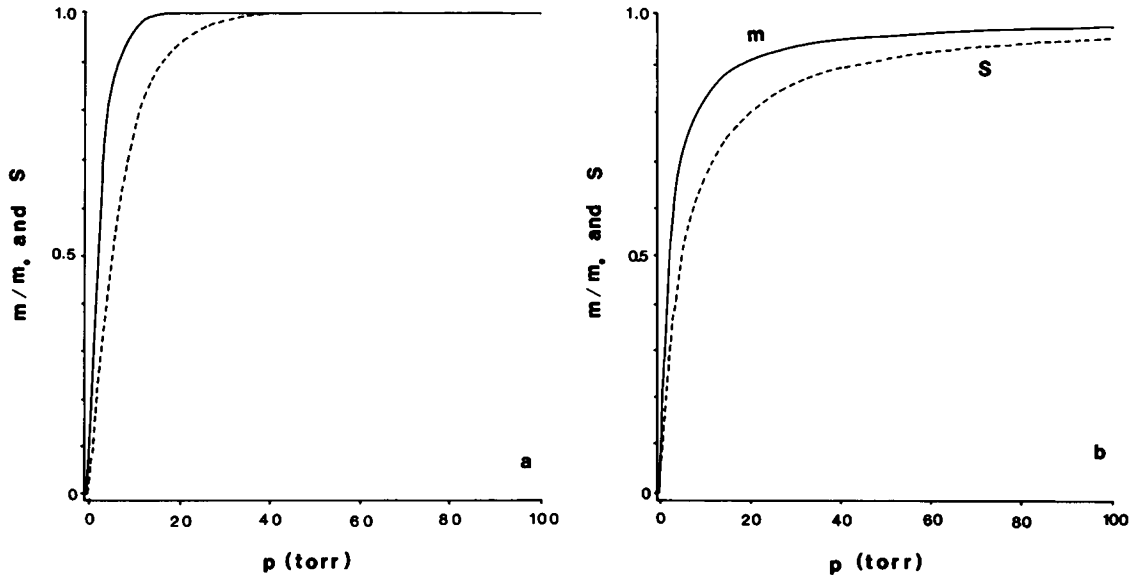

FIGURE 1 $S = S(p)$ (*dashed lines*) and $m = m(p)$ (*solid lines*) relations. S, fractional saturation of myoglobin; m, local or tissue metabolic rate (normalized to m_0 for convenience); p, local or tissue partial pressure of oxygen. (*a*) Exponential ($m_2 = S_2 = 1$ in Eqs. 8 and 9); (*b*) hyperbolic ($n_m = n_S = 1$). In both *a* and *b* $p_{50,m} = 2$ and $p_{50,S} = 5$ torr.

tively:

$$J_{O_2} = \sigma_{O_2} D_{O_2} \frac{dp}{dr}$$

and

$$J_{MbO_2} = c_{Mb} D_{Mb} \frac{dS}{dp} \frac{dp}{dr}. \quad (12)$$

Integration of Eq. 8, which specifies the oxygen concentration–consumption relation, over the muscle cross-sectional area yields the metabolic rate of oxygen consumption averaged through the muscle. Explicitly, the mean metabolic rate of the muscle is given by:

$$\overline{m} = \frac{2}{r_0^2} \int_0^{r_0} r \cdot m[p(r)]\, dr, \quad (13)$$

where r_0 is the radius of the muscle. (Note that Eq. 13 differs from Eq. 5 of Loiselle [1982], which is in error.) To achieve the objectives stated in the Introduction, it is necessary to calculate the average metabolic rate–muscle radius relation [$\overline{m} - \overline{m}(r_0)$] both in the presence ($c_{Mb} > 0$) and the absence ($c_{Mb} = 0$) of myoglobin-facilitated oxygen diffusion. It is then possible to predict the magnitude of the myoglobin contribution in vitro and decide whether the observed $\overline{m} - \overline{m}(r_0)$ relation (Loiselle and Gibbs, 1983) can be explained on the basis of some limitation of oxygen diffusion in muscles of large diameter. No attempt was made to find an optimal fit to the observed $\overline{m} - \overline{m}(r_0)$ data. Instead the model was evaluated for a range of parameter values typically encountered in experiments where the behavior of isolated papillary muscle is studied in vitro.

RESULTS

Eq. 7 was solved for a variety of parameter values simulating both the presence ($c_{Mb} = 2.8 \times 10^{-7}$ mol · cm^{-3}) and absence ($c_{Mb} = 0$) of myoglobin. Typical values for the external partial pressure of oxygen (p_o) were 20, 40, 100, 150, 380, and 722 torr. These choices correspond to values of local venous PO_2, mixed venous PO_2, arterial PO_2, and PO_2 values in a saline bath aerated with 20, 50, and 95% O_2, respectively. Typical values for m_0, the metabolic rate in an infinitesimal annulus of tissue on the surface of the muscle, were 5, 10, and 25 mW/g. These choices correspond approximately to observed values of resting heat production of rabbit (Loiselle and Gibbs, 1983) and rat (Loiselle and Gibbs, 1979; Loiselle, 1985*b*) papillary muscles in vitro, and an estimated value for the basal rate of oxygen consumption of rat myocardium in vivo (Loiselle and Gibbs, 1979), respectively. Typical p_{50} values were 1, 2, 5, and 20 torr for metabolism and 2, 5, 10, and 40 torr for fractional saturation of myoglobin. Note that 1 torr is the equivalent of an oxygen concentration of 1.2 μmol · l^{-1} at 37°C, a value approximating the p_{50} of oxygen consumption in vitro (Jöbsis, 1972; Wilson et al., 1977).

The integer parameters m_2 and S_2, or n_m and n_S, the exponents in the sigmoidal $m = m(p)$ and $S = S(p)$ relations (Eqs. 8 and 9), were usually unity (yielding exponential or hyperbolic relations, respectively) but were varied over the range from 1 to 5. The mean rate of metabolism ($\overline{m}$) was explored over values of muscle radii (r_0) ranging from 0.1 to 2.0 mm. A large number of computer simulations were performed corresponding to different values of the above parameters. Only the minimal number of these results consistent with describing the behavior of the model and exemplifying the major conclusions are presented.

The behavior of the model (Eq. 7) is shown in Fig. 2 for two examples of exponential and hyperbolic dependence of metabolic rate and oxymoglobin saturation upon local PO_2. The solutions yield the profiles of oxygen partial pressure

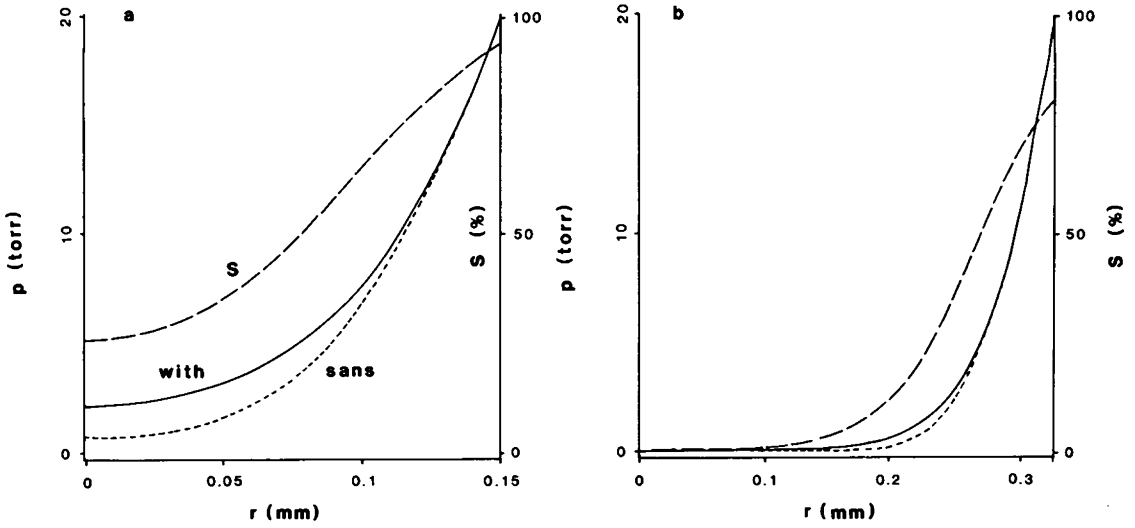

FIGURE 2 $S = S(r)$ (*broken sigmoidal curve*) and $p = p(r)$ (*monotonic curves: solid line,* with Mb; *dashed line,* sans Mb) relations resulting from solution of Eq. 7. S, fractional saturation of myoglobin (right-hand ordinate); p, local or tissue partial pressure of oxygen (left-hand ordinate); r, radial location from central axis ($r = 0$) to periphery ($r = r_0$). $p_0 = 20$ torr; $r_0 = 0.150$ and 0.326 mm in *a* and *b*, respectively; remaining simulation parameters same as for Fig. 1.

(p) and myoglobin saturation (S) throughout the cross-section of the muscle. A low value (20 torr) of oxygen partial pressure at the surface of the muscle was simulated to demonstrate a sizeable effect of myoglobin. The myoglobin saturation profile, $S = S(r)$, tends toward a plateau value of full saturation near the periphery of the muscle. Myoglobin desaturation occurs toward the center of the muscle to a variable extent depending on the simulation parameters. Whether in the presence or absence of myoglobin and regardless of the form of the dependence (exponential, hyperbolic, or sigmoidal), the resulting $p = p(r)$ relations fall monotonically from p_0, the oxygen partial pressure on the surface of the muscle (at $r = r_0$) to p_a, the value at the center of the muscle (at $r = 0$). For given values of r_0 and p_0, the calculated $p = p(r)$ relations were virtually identical for the exponential and hyperbolic forms of the $m = m(p)$ and $S = S(p)$ relations (Eqs. 8 and 9). The difference between *a* and *b* in Fig. 2 is almost entirely due to the difference in r_0 (0.15 and 0.33 mm, respectively). The partial pressure of oxygen on the axis (p_a) was in every case elevated in the presence of myoglobin.

A more convenient way to examine the contribution of myoglobin is presented in Fig. 3 where the total oxygen flux in the presence of myoglobin (J) has been partitioned into its simple (J_{O_2}) and facilitated (J_{MbO_2}) components (*a* and *b*). Note that both of these components of flux in the presence of myoglobin (like the flux of oxygen in the absence of myoglobin) decline to zero on the central longitudinal axis of the muscle ($r = 0$) as required by radial symmetry. The relative contribution of myoglobin-facilitated oxygen flux (i.e., J_{MbO_2}/J) has also been plotted in Fig. 3 (*c* and *d*). Whereas the facilitated oxygen flux is typically quite small in absolute terms, it may account for a sizeable fraction of the total oxygen flux at various locations within a muscle. Examination of Fig. 3 *d* shows that at the center of the simulated muscle of radius 0.33 mm, myoglobin accounts for ~65% of the total oxygen flux. But comparison with Fig. 2 *b* (same simulation parameters) shows this to be a rather misleading statement. In fact, myoglobin has been unable to prevent the oxygen concentration from falling to near zero values throughout the central core of the muscle. Whereas the relative contribution of myoglobin in this region is considerable, its absolute contribution is not.

It is more instructive to index the contribution of myoglobin by calculating its effect on the partial pressure of oxygen on the axis (p_a). This effect is shown in Fig. 4 for the same simulation parameters as used in Figs. 2 and 3. Over a wide range of muscle radii (0.05–0.25 mm), axial oxygen concentration is higher in the presence of myoglobin. At a muscle radius of 0.13 mm, it is slightly more than twice as high with as without myoglobin. But at double this radius (0.26 mm) or greater, not even the presence of myoglobin can prevent p_a from falling to near zero values. Note, too, the extreme similarity of results in Fig. 4 between *a* and *b* corresponding, respectively, to exponential and hyperbolic dependence of metabolism and myoglobin saturation upon oxygen partial pressure. The computed $p_a = p_a(r_0)$ relations resulting from exponential dependence (*a*) lie marginally to the left of those based on hyperbolic dependence (*b*). The slight difference in form of the underlying saturation relations (Fig. 1) leads to an even smaller difference in axial partial pressure of oxygen (Fig. 4).

Most of the above results have arisen from the solution of Eq. 7 for some fixed value of r_0, the muscle radius, and have been presented to show some of the consequences of

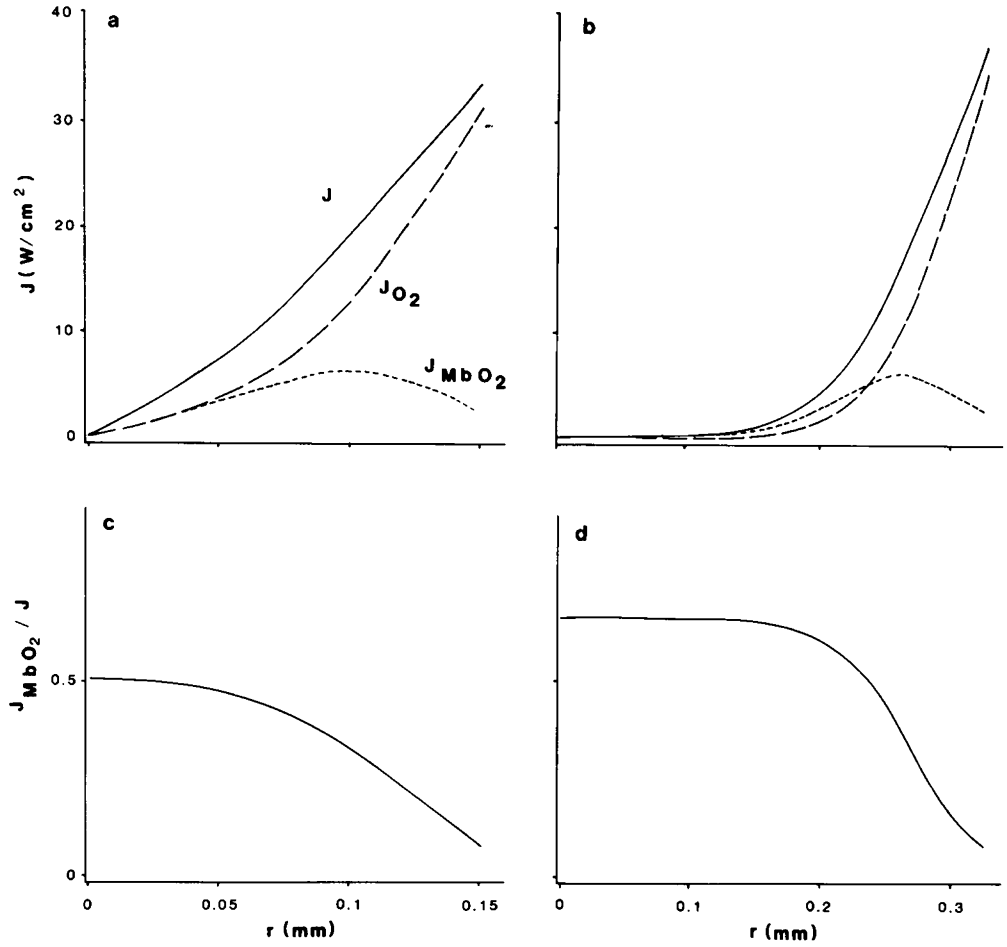

FIGURE 3 Components of oxygen flux (J, W/cm^2, assuming 20 kJ/liter O_2) as a function of radial location. (*a* and *b*) J (total O_2 flux, *solid line*) = J_{O_2} (simple O_2 flux, *dashed line*) + J_{MbO_2} (myoglobin-facilitated O_2 flux, *broken line*). (*c* and *d*) J_{MbO_2}/J = fraction of total flux contributed by Mb. Simulation parameters as in Fig. 2.

incorporating a myoglobin term. An additional objective of this study, however, was to compare the basal metabolism–muscle radius relation ($\overline{m} = \overline{m}(r_0)$) predicted by the model with that experimentally observed. This comparison is shown in Fig. 5 for various values of p_0 and for various $m = m(p)$ and $S = S(p)$ relations. In each case (Fig. 5, *a–d*), the metabolic rate at the periphery of the muscle, m_0, was set to 5 mW/g since only this value yielded simulated $\overline{m} = \overline{m}(r_0)$ relations which approximated the observed data. The experimentally observed data are those of Loiselle and Gibbs (1983) for the rate of resting heat production of rabbit papillary muscles bathed in 95% O_2 (722

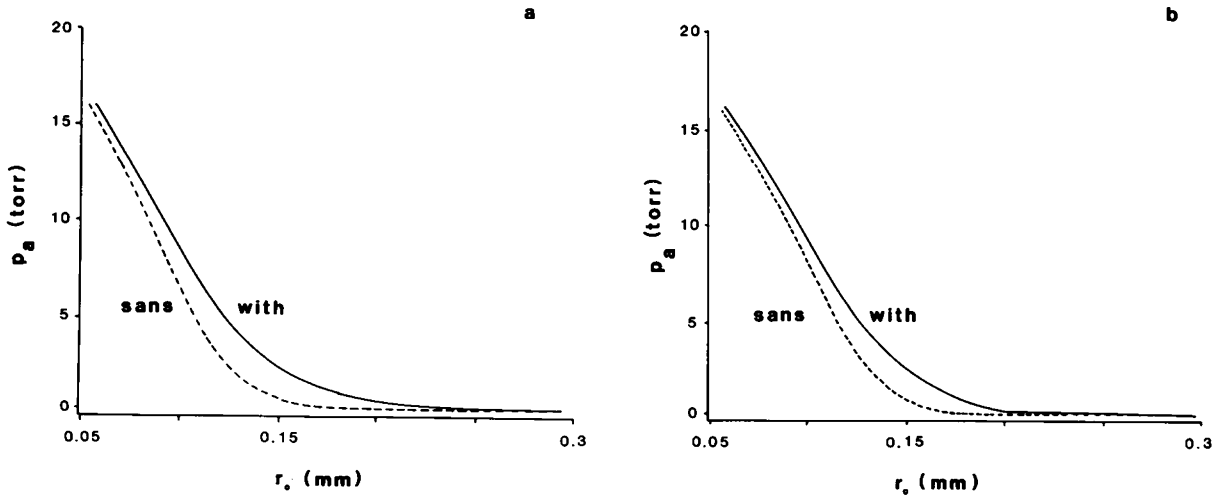

FIGURE 4 Partial pressure of oxygen on the axis (p_a) in the presence (with) and absence (sans) of myoglobin for muscles of various radii (r_0). (*a*) Exponential dependence; (*b*) hyperbolic dependence of m and S on p (Eqs. 8 and 9). Simulation parameters as in Fig. 2.

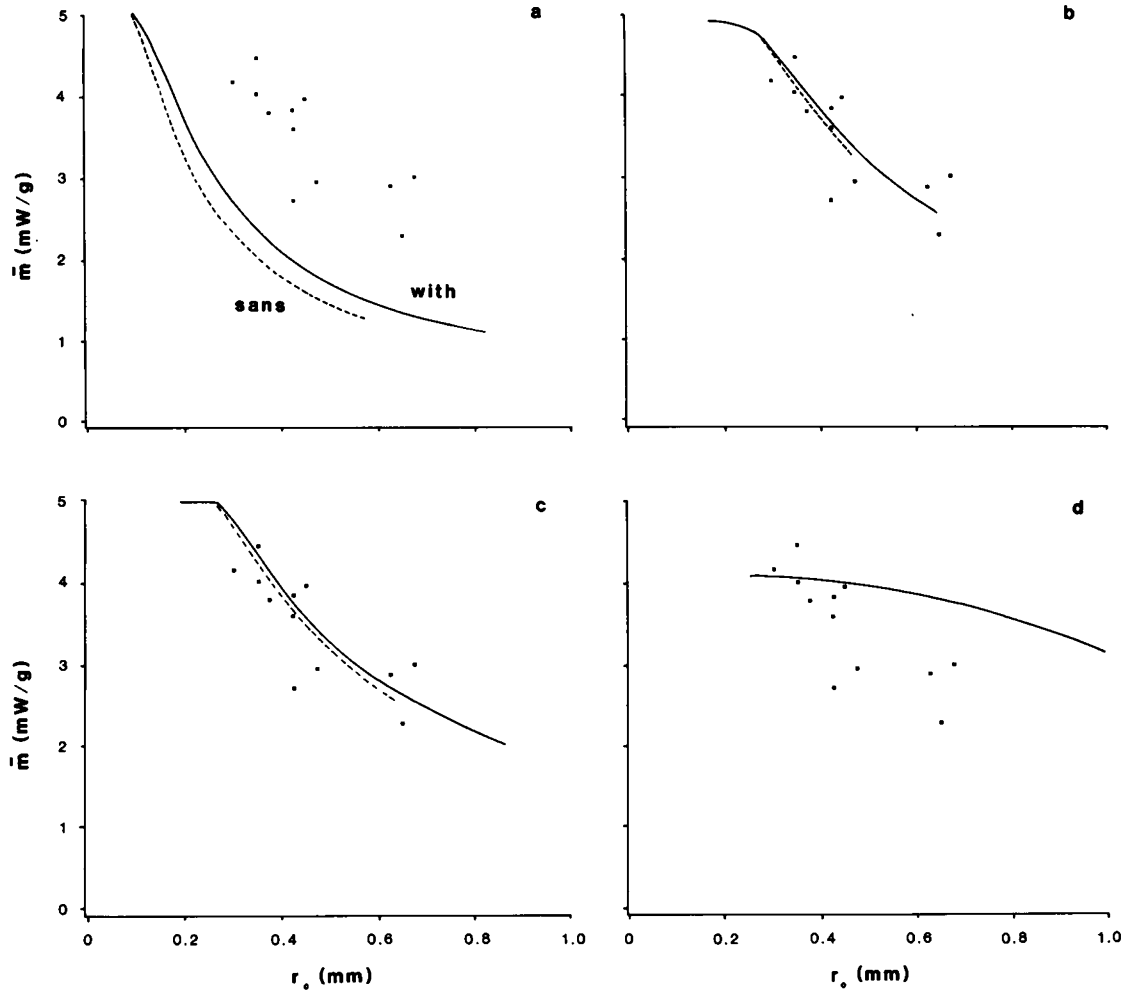

FIGURE 5 $\overline{m} = \overline{m}\ (r_o)$ relations: with Mb (*solid line*), sans Mb (*dashed line*), and experimentally observed (Loiselle and Gibbs, 1983) (*squares*). $\overline{m}$, mean metabolic rate averaged over the cross-section of the muscle (Eq. 13); r_o, muscle radius. In *a–c*, $p_{50,m}$ = 2 torr and $p_{50,S}$ = 5 torr; in *d* the corresponding values are 100 and 150 torr; m_o = 5 mW/g throughout; p_o = 20, 100, 100, and 722 torr, respectively. (*a* and *c*) Exponential; (*b* and *d*) hyperbolic $m = m(p)$ and $S = S(p)$ relations.

torr) at 30°C. These data (shown by squares) are repeated in each panel of the figure for convenience.

It proved impossible to simulate closely the observed $\overline{m} = \overline{m}\ (r_o)$ relation using p_o = 722 torr. Fig. 5 *d* shows an approximation, achieved by recourse to extreme p_{50} values ($p_{50,m}$ = 100 torr, $p_{50,S}$ = 150 torr), which moved the simulated $\overline{m} = \overline{m}\ (r_o)$ relation to the left but at the expense of flattening it considerably. Using realistic p_{50} values, a reasonable fit of the theoretical to the observed data (Fig. 5, *b* and *c*) could be achieved only by lowering p_o to 100 torr, a value well below that used experimentally. Lowering the external oxygen partial pressure even further moved the simulated basal metabolism–muscle size relation to the left of the observed data (Fig. 5 *a*) independent of the form (exponential or hyperbolic) of the underlying metabolism and saturation relations (compare Fig. 5 *b* with Fig. 5 *c*). Qualitatively, the shapes of the observed and simulated basal metabolic rate–muscle radius relations are similar; quantitatively, agreement cannot be achieved without recourse to extreme simulation parameters.

Fig. 5 also clearly demonstrates the insensitivity of the simulated $\overline{m} = \overline{m}\ (r_o)$ relation to the presence or absence of myoglobin. Thus when p_o = 722 torr (Fig. 5 *d*), the relation simulated in the presence of myoglobin superimposes on that corresponding to its absence, despite a 50 torr separation in p_{50} values. Likewise at p_o = 100 torr (Fig. 5, *b* and *c*), the presence of myoglobin has a negligible effect upon the calculated $\overline{m} = \overline{m}\ (r_o)$ relation. Even when p_o is reduced to the extreme value of 20 torr, such that myoglobin can transport a sizeable fraction of the total oxygen (Fig. 3) and hence can considerably increase the partial pressure of oxygen on the central axis of the muscle (Fig. 4), the resulting mean metabolic rate of the muscle is little influenced (Fig. 5 *a*).

DISCUSSION

This study proposes a model of simple and myoglobin-facilitated oxygen transport into isolated papillary muscles and examines its behavior. The model assumes a nonlinear relation between the local metabolic rate of oxygen con-

sumption and the local tissue partial pressure of oxygen. Total oxygen flux is partitioned into two components: the simple diffusion of molecular oxygen through the myoplasm and its facilitated diffusion by binding to myoglobin. The contribution of facilitation to the total diffusion of oxygen is assessed by comparing the behavior of the model with and without myoglobin.

Behavior of the Model

In the simulated papillary muscle, the PO_2 falls smoothly from p_o on the periphery to p_a on the axis. Myoglobin reduces the extent of the fall. In doing so it becomes progressively desaturated toward the central axis (Fig. 2). Consider a large muscle. At its periphery myoglobin will be at or near full saturation so net flux of oxymyoglobin is low. At the center of this large muscle, the myoglobin is largely desaturated so the net flux of oxymyoglobin is again low. But since the flux of molecular oxygen has become negligible here, the relative contribution of myoglobin facilitation is proportionately higher. This behavior is shown in Fig. 3. In *a* and *b* the absolute flux of oxymyoglobin in both simulated muscles is low at their centers; in *c* and *d* it is shown, nevertheless, to dominate the simple oxygen flux in this region. As a consequence of this behavior, the absolute magnitude of the facilitated oxygen flux passes through a maximum somewhere between the periphery of the muscle and its core (Fig. 3, *a* and *b*). As shown in Fig. 4, the presence of myoglobin can be expected to increase the PO_2 at the center of a papillary muscle by a factor of two or more. This result is consistent with those from models of either solid (Murray, 1974) or Krogh-cylinder geometry (Fletcher, 1980) in which metabolism is independent of PO_2.

Despite the dramatic effect of myoglobin upon oxygen flux within the hypoxic central region of the simulated muscle, the influence of myoglobin becomes negligible when averaged over the entire cross-sectional area. This is shown in Fig. 5 where the various basal metabolism–muscle radius relations in the presence of myoglobin are virtually indistinguishable from those in its absence. This result is true whether the underlying forms of the oxygen consumption–PO_2 and oxymyoglobin saturation–PO_2 relations are assumed to be exponential (Eqs. 8a and 9a) or to be described by the Hill equation (Eqs. 8b and 9b) in either its general or its limiting hyperbolic form. As a consequence, incorporating myoglobin into the theoretical model has failed to shed any light on the experimentally determined basal metabolism–muscle size relation.

Experimentally, it is only possible to measure the average rate of oxygen consumption of any tissue preparation as a function of oxygen partial pressure. But the tissue preparation necessarily has thickness that itself diminishes the oxygen flux. Wittenberg et al. (1975) measured the rate of respiration of both thick (3 mm) slabs and thin (0.25 mm) polygonal-shaped fiber bundles of pigeon breast muscle exposed to varying PO_2 environments from 5 to 200 torr. Oxygen consumption was ~25% greater in the thinner preparations and, in both cases, fell to half-maximal at a PO_2 of ~40 torr. Hence the true (i.e., tissue thickness–independent) half-maximal rate must lie to the left of this value. For the current model the dependence of mean rate of oxygen consumption (i.e., averaged throughout the muscle cross-section) upon external PO_2 (the $\overline{m} = \overline{m}(p_o)$ relation) was solved for a variety of muscle radii. Results for a particular choice of parameters are shown in Fig. 6. Note that the sigmoidal nature of the underlying $m = m(p)$ relation is evident in the calculated $\overline{m} = \overline{m}(p_o)$ relations. Note too that for any given PO_2, oxygen consumption is less in thicker muscles.

The particular parameters used to generate the data of Fig. 6 were chosen because the resulting graphs closely resemble those in Fig. 4 of Wittenberg et al. (1975). Quite different parameters would be required to fit the $\overline{m} = \overline{m}(p_o)$ data of Cole et al. (1978) for the isolated, isovolumetrically contracting, fluocarbon-perfused dog heart. In this preparation m_o appears to be ~100 mW/g in the range 600–700 torr, reducing to half maximal at an oxygen partial pressure of ~200 torr. So for both real and simulated preparations, the external PO_2 that yields half-maximal oxygen consumption increases with both the inherent rate of oxygen consumption (m_o) and the effective thickness of the preparation (r_o). But as can be seen in Fig. 6, the presence of myoglobin (even when a 10-fold increase in concentration is assumed) enhances only slightly the mean oxygen consumption at any oxygen concentration. Even this slight enhancement is an overestimation since no account was taken of the fact that myoglobin diffusivity declines with increasing myoglobin concentration (Kreuzer, 1970; Wittenberg, 1970).

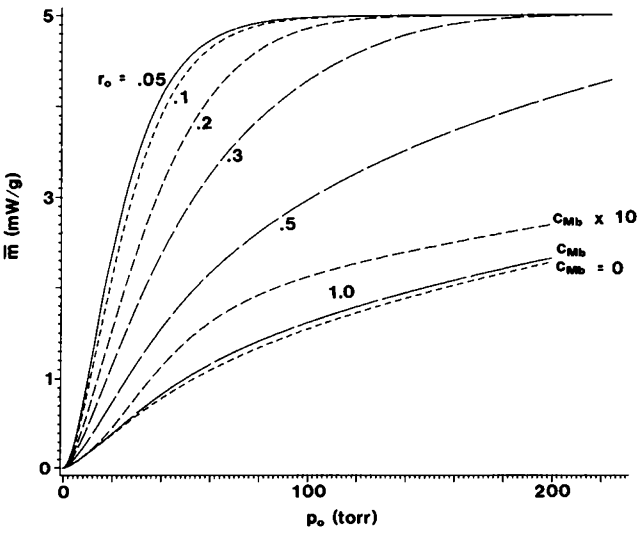

FIGURE 6 $\overline{m} = \overline{m}(p_o)$ relations for muscles of radius 0.05–1.0 mm. Simulation uses Eq. 8a (m_o = 5 mW/g; $p_{50,m}$ = 20 torr, m_2 = 2) and Eq. 9a ($p_{50,S}$ = 50 torr, S_2 = 5). c_{Mb}, concentration of myoglobin (2.8×10^{-7} mol·cm^{-3}). Note: for r_o = 1.0 mm simulation only, effect of sans Mb (c_{Mb} = 0) and 10-fold increase in c_{Mb} also shown for comparison.

Thus whether assessed by the basal metabolism–muscle size relation (Fig. 5) or by the basal metabolism–external PO_2 relation (Fig. 6), myoglobin is seen to make but a modest contribution to respiration in the isolated papillary muscle. This result is surprising and warrants a critical examination of the assumptions underlying the model.

Assumptions of the Model

The steady-state model of oxygen transport used in this study (Eq. 7) contains two homogeneity assumptions. First, it is assumed that the muscle tissue is homogeneous throughout its cross-section and contains neither plasmalemmal nor intracellular membranes. Gonzalez-Fernandez and Atta (1982) have shown that the presence of equally spaced myoglobin-impermeable membranes of infinitesmial thickness can severely attenuate the facilitated flux of oxygen. The incorporation of diffusion barriers into the current model could thus only lessen the contributions of myoglobin observed above (Figs. 2–5), thereby strengthening the proposition that its role is minimal.

Second, the model assumes that the sites of oxygen consumption are distributed homogeneously rather than being spatially localized within the mitochondria. Mainwood and Rakusan (1982) use a Krogh-cylinder model in which each cylindrical muscle cell is surrounded by four capillaries and mitochondria are either evenly distributed throughout the cell or are clustered peripherally, in a 3-μm annulus, near the capillaries. The latter case naturally leads to a much higher partial pressure of oxygen in the central region of the cell since mitochondria, and hence oxygen consumption, are absent. In this model the burden of energy transport into the muscle core, beyond the 3-μm peripheral layer, is shifted from oxygen to the creatine phosphate shuttle. Hence it is even less likely that myoglobin could make a significant contribution to the net transport of energy in such a model since its effectiveness would be restricted to the outermost 3-μm layer. Its contribution would be further diminished if the rate of oxygen consumption were to depend upon the local intramitochondrial partial pressure of oxygen as in the current model.

Implications of the Model

In isolated papillary muscles, the rate of basal heat production is observed to decline with increasing muscle diameter (Loiselle and Gibbs, 1983; Gibbs et al., 1984). Fig. 5 shows that such behavior cannot be due, in any simple manner, merely to inadequate oxygenation of large muscles. This statement is true whether or not myoglobin is available to facilitate the diffusive transport of oxygen.

From the above simulations, it may be concluded that myoglobin plays a nonsignificant role in the oxygenation of isolated muscle preparations commonly used in vitro. In support of this conclusion, Cole et al. (1978) found that poisoning myoglobin, by converting it to the nonfunctional ferric state through use of sodium nitrite, had no effect upon the rate of oxygen consumption of the isolated, beating dog heart when the perfusate oxygen pressure exceeded 150 torr. Similarly, Wittenberg et al. (1975), using a variety of poisoning procedures, could demonstrate a significant contribution by myoglobin to the oxygen consumption of thin muscle fiber bundles only if PO_2 was less than ~120 torr. Two recent reports confirm this result. Kenwright and Loiselle (1986), using an isolated, Langendorff-circulated, saline-perfused guinea-pig heart in a state of electrical and mechanical arrest, found that nitrite poisoning of myoglobin reduced oxygen consumption only when arterial PO_2 was 70 torr or less. Similarily, Taylor et al. (1986), using nuclear magnetic resonance techniques, showed a diminution of high energy phosphate metabolism in the isolated rat heart, subsequent to inhibition of myoglobin function, only when arterial oxygen concentration was low (100 μmol$\cdot$l^{-1}).

In conclusion, exploration of the diffusion model shows that myoglobin can make a significant contribution to muscle oxygen consumption in vitro provided that the preparation is thin, has a high inherent rate of oxygen consumption, and is bathed in a medium of low PO_2 (corresponding to common arterial values or less). These three requirements are rarely obtained, simultaneously, in vitro. In fact, experimentalists usually go to great lengths to ensure the PO_2 is far in excess of its usual arterial value. It is this experimental gambit that renders the contribution of myoglobin negligible in vitro, a situation that in no way diminishes its undoubted role in vivo.

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